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10/798,111	03/10/2004	Dario Norberto R. Carrara	88066-7900	5916

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EXAMINER	
SCHLIENTZ, NATHAN W	
ART UNIT	PAPER NUMBER
1616	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/798,111	CARRARA ET AL.	
	Examiner	Art Unit	
	Nathan W. Schlientz	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 February 2011*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-7,11,13,17-19,29,37,40-42,46,47,56-58,60-63 and 67-72* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-7,11,13,17-19,29,37,40-42,46,47,56-58,60-63 and 67-72* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1)☐ Notice of References Cited (PTO-892)

2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3)☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/9/11 and 2/10/11*.

4)☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

5)☐ Notice of Informal Patent Application

6)☐ Other: _____.

DETAILED ACTION

Status of Claims

Claims 1, 3-7, 11, 13, 17-19, 29, 37, 40-42, 46, 47, 56-58, 60-63 and 67-72 are pending and are presently examined herein on the merits for patentability. No claim is allowed at this time.

It is noted that claim 7 recites "...and the permeation enhancer is a monoalkyl ether of diethylene glycol." However, claim 1 already recites that the permeation enhancer is a monoalkyl ether of diethylene glycol. Therefore, the recitation in claim 7 is superfluous. It's also noted that claim 37 recites "consisting essentially of" whereas dependent claim 46 recites "further comprising". The term "further comprising" implies that the parent claim recited "comprising". It is recommended that claim 47 recite "includes".

Information Disclosure Statement

1. The information disclosure statements (IDS) submitted on 9 February 2011 and 10 February 2011 were filed after the mailing date of the non-final Office Action on 23 December 2010. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statements have been considered by the examiner.

Withdrawn Rejections

2. Rejections and/or objections not reiterated from the previous Office Action are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set of rejections and/or objections presently being applied to the instant application.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claim 67 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 67 recites the limitation "the ***gel*** formulation of claim 37" in the 2nd and 3rd lines. There is insufficient antecedent basis for this limitation in the claim. Claim 37 does not require the formulation to be a gel. This is further evidenced by claim 47 that recites different forms for claim 37, which includes gel and many other forms.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in Graham v. John Deere Co., 383 U.S. 1,148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

4. Claims 1, 3-7, 11, 13, 17-19, 29, 37, 40-42, 46, 47, 56-58, 60-63 and 67-72 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gray et al. (WO 02/22132; US 7,030,104; and US 2003/0181430), in view of Dudley et al. (US 6,503,894) and Wang et al. (The Journal of Clinical Endocrinology and Metabolism, 2000).

Determination of the scope and content of the prior art

(MPEP 2141.01)

Gray et al. teach in Table 1 gel formulations (Reference G29-287, G29-299 and Tx11323) for percutaneous administration wherein the gels comprise:

REFERENCE	G29-287	G29-299	Tx11323 batch-12
NAc (nomegestrol acetate)	0.4	0.4	—
Estradiol	—	0.1	0.1
Carbopol 1342 or 1382	0.5	0.5	0.5
Propyleneglycol	6	6	6
Transcutol	5	5	5
Solketal			
EDTA	0.05	0.05	0.05
Triethanolamine	0.3	0.3	0.3
Demineralized water	42.75	42.65	43.05
95° Ethanol	45	45	45

Gray et al. also teach topically administering two gel formulations A and B (Table 5), depicted below, to women by spreading 3 g of gel per day over 400 cm^2 (col. 13, ln. 1-25).

TABLE 5

formula of the 2 gels used for pharmacokinetic trials in women

	Gel A	Gel B
Nomegestrol acetate	0.40	0.40
Propylene glycol	8.00	8.00
Solketal	3.00	3.00
Carbopol 980	0.60	
Carbopol 1382		0.50
EDTA	0.05	0.05
TEA	0.24	0.30
95° Ethanol	45.00	45.00
Demineralized water	42.69	42.73

Gray et al. further teach that topically administering gel TX11323 (shown above) at a rate of 3 g of gel on a body area of 400 cm^2 leads to plasmatic levels of estradiol at the equilibrium of approximately 40 pg/ml, which are located in the area of effective plasmatic concentrations of estradiol as these are comprised between 30 and 60 ng/ml (col. 14, ln. 1-6). Gray et al. teach that estradiol gels likely to produce satisfactory clinical results must present during in vitro tests of percutaneous passage cumulative quantities of estradiol at 24 hours of greater than 1.05 µg without exceeding 2.1 µg so as not to induce hyperestrogenosis (col. 14, ln. 7-15).

Therefore, Gray et al. teach a gel comprising:

- a hormone (nomegestrol acetate, a progestin, at 0.4 wt.% (G29-287); estradiol, an estrogen, at 0.1 wt.% (Tx11323 batch-12); or a combination thereof (G29-299));
- a gelling agent (Carbopol 1342 or 1382) at 0.5 wt.%;
- an alkanol (95° ethanol) at 45 wt.%;

- a polyalcohol (propylene glycol) at 6 wt.%;
- a permeation enhancer (Transcutol® (diethylene glycol monoethyl ether), or Solketal) at 5 wt.%;
- a neutralizing agent (triethanolamine) at 0.3 wt.%;
- a sequestering agent (EDTA) at 0.05 wt.%; and
- water at 42.65-43.05 wt.%.

Gray et al. teach administering the gels to women for to determine the pharmacokinetic behavior or percutaneous administration for hormonal treatment of perimenopause and menopause as well as ovarian hormonal deficiencies (col. 1, ln. 15-19; col. 2, ln. 12-16; and col. 14, ln. 1-15).

Ascertainment of the difference between the prior art and the claims

(MPEP 2141.02)

Gray et al. do not specifically recite that the active ingredient is testosterone, as instantly claimed. However, Dudley et al. teach topical formulations for treating hypogonadism in males comprising androgenic steroids or progestogens (col. 11, ln. 63 to col. 12, ln. 1; and Table 5). Dudley et al. teach that the composition comprises an androgenic steroid, such as testosterone, methyltestosterone and/or methandrostenolone (col. 11, ln. 63 to col. 12, ln. 1); a C1-C4 alcohol, such as ethanol (col. 12, ln. 17-18); a penetration enhancer, such as diethylene glycol monoethyl ether (col. 12, ln. 54-55); a thickener, such as Carbopol (col. 12, ln. 60-67); and water (col. 12, ln. 17-22). Dudley teaches a testosterone gel named AndroGel® that comprises 1 wt.% testosterone (Table 5). Therefore, it would have been well within the purview of one of ordinary skill in the art to use the appropriate hormone, such as testosterone at 1 wt.%, in the formulations of Gray et al. for treating a person for hypogonadism.

With regard to instant claims 58 and 63, Gray et al. do not teach a kit comprising a container that retains their compositions and includes a pump for dispensing a predetermined dosage or volume of the formulation upon demand. However, delivering hormone gels via actuation of a pump is readily known in the art, as shown by Wang et al. wherein hydroalcoholic gels containing 1 wt.% testosterone were packaged in multidose bottles with an actuator pump for treatment of hypogonadal males (pg. 2840, right column, "T gel and patch"). Also, Dudley et al. teach a hand-held pump capable of delivering about 2.5 g of testosterone gel with each actuation as well as foil packets, wherein the composition is dispensed from the containers via a hand pump to deliver accurate but incremental amounts of gel to the body (Example 2).

With regard to instant claims 69-72, Gray et al. teach the their topical composition comprises a hormone; a solubilizing agent such as an ethanol/water/propylene glycol ternary mixture in which the amount of ethanol is 30 to 60 wt.%, more particularly 40 to 60 wt.%, in particular 40 to 50 wt.% of the total composition and that of propylene glycol is 2 to 20 wt.%, in particular 6 to 12 wt.% of the total composition (col. 3, ln. 20-62; claim 10); an absorption promoting agent, such as diethylene glycol monoethyl ether in an amount of 2 to 12 wt.% of the total composition (col. 3, ln. 63 through col. 4, ln. 27); a gelling agent in an amount of 0.3 to 1 wt.% of the total composition (col. 4, ln. 34 through col. 5, ln. 25). Also, Dudley et al. teach that their compositions may contain about 0.1 to about 10.0 wt.% of testosterone, about 0.1 to about 5.0 wt.% gelling agent, about 0.1 to about 5.0 wt.% isopropyl myristate

(penetration enhancer), and about 30.0 to about 98.0 wt.% ethanol (col. 13, ln. 36-43; and claims 1, 2, 4, 6-8, 10, 14, 17-19, 23-25, 31, 32, 37 and 38).

Finding of prima facie obviousness

Rational and Motivation (MPEP 2142-43)

Therefore, it would have been *prima facie* obvious for one of ordinary skill in the art at the time of the invention to treat hypogonadism with the compositions of Gray et al., using 1 wt.% testosterone, and as the penetration enhancer diethylene glycol monoethyl ether, as reasonably taught by Dudley et al. Further, it would have been *prima facie* obvious for one of ordinary skill in the art at the time of the invention to package the hydroalcoholic gels into multidose bottles with an actuator pump for dispensing predetermined dosages, as reasonably taught by Wang et al. and Dudley et al.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Response to Arguments

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208

USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Applicant argues on page 11 that Gray is specific for cutaneous topical preparations containing a synthetic progestogen and a natural or synthetic estrogen. Therefore, a person of ordinary skill in the art, following the teachings of Gray, will not choose to replace its active agents with testosterone mentioned by Dudley. However, the examiner respectfully asserts that Dudley et al. teach topical gel formulations for percutaneous administration comprising at least one active pharmaceutical agent, such as androgenic steroids (e.g., testosterone) and progestogens. Therefore, Dudley et al. teach substituting testosterone and progestogens in topical gel formulations for percutaneous administration. Thus, a person having ordinary skill in the art would have motivation to substitute testosterone in the place of progestogens with a reasonable expectation of success.

Applicant further argues that there is no expectation of success to replace progestogen and estradiol taught in Gray with testosterone disclosed in Dudley. As supported by a previously submitted research paper (P. Karande et al., *High Throughput Screening of Transdermal Formulations,* Pharmaceutical Research, vol. 19, no. 5, May 2002, pp. 655-660), more than 200 chemical enhancers including surfactants, fatty acids, fatty alcohols, and organic solvents have been used in attempts to increase transdermal drug transport. Dudley discloses that fatty acid derivatives, in particular, isopropyl myristate, are preferred penetration enhancers for the testosterone formulation (see the AndroGel® formulation in Table 5 of Dudley). Even though Dudley

does mention other compounds such as diethylene glycol monomethyl ether in his listing of permeation enhancers, he attributes no preference to that compound. Thus, one of ordinary skill in the art, reading Dudley, will not be taught or motivated to select diethylene glycol monomethyl ether as taught in Gray in place of isopropyl myristate as the transdermal enhancer for the active agent testosterone as presently claimed. Furthermore, Dudley does not even mention diethylene glycol monoethyl ether as recited in claims 69-72.

However, the examiner directs attention to MPEP 2123(I) and (II):

> "The use of patents as references is not limited to what the patentees describe as their own inventions or to the problems with which they are concerned. They are part of the literature of the art, relevant for all they contain." *In re Heck*, 699 F.2d 1331, 1332-33, 216 USPQ 1038, 1039 (Fed. Cir. 1983) (quoting *In re Lemelson*, 397 F.2d 1006, 1009, 158 USPQ 275, 277 (CCPA 1968)).
>
> A reference may be relied upon for all that it would have reasonably suggested to one having ordinary skill the art, including nonpreferred embodiments. *Merck & Co. v. Biocraft Laboratories*, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989). See also *Upsher-Smith Labs. v. Pamlab, LLC*, 412 F.3d 1319, 1323, 75 USPQ2d 1213, 1215 (Fed. Cir. 2005); *Celeritas Technologies Ltd. v. Rockwell International Corp.*, 150 F.3d 1354, 1361, 47 USPQ2d 1516, 1522-23 (Fed. Cir. 1998) (The court held that the prior art anticipated the claims even though it taught away from the claimed invention. "The fact that a modem with a single carrier data signal is shown to be less than optimal does not vitiate the fact that it is disclosed.").
>
> Disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or nonpreferred embodiments. *In re Susi,* 440 F.2d 442, 169 USPQ 423 (CCPA 1971). "A known or obvious composition does not become patentable simply because it has been described as somewhat inferior to some other product for the same use." *In re Gurley*, 27 F.3d 551, 554, 31 USPQ2d 1130, 1132 (Fed. Cir. 1994). Furthermore, "[t]he prior art's mere disclosure of more than one alternative does not constitute a teaching away from any of these alternatives because such disclosure does not criticize, discredit, or otherwise discourage the solution claimed...." *In re Fulton*, 391 F.3d 1195, 1201, 73 USPQ2d 1141, 1146 (Fed. Cir. 2004).

Dudley et al. clearly list both isopropyl myristate and diethylene glycol monomethyl ether as penetration enhancers suitable for use in their invention. Also, Gray et al. teach 5 wt.% Transcutol (monoethyl ether of diethylene glycol) as a suitable penetration enhancer/absorption promoting agent. One of ordinary skill in the art would reasonably have chosen 5 wt.% monoethyl ether of diethylene glycol as the penetration enhancer with the expectation that the penetration enhancer would effectively accelerate the delivery of the testosterone through the skin.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nathan W. Schlientz whose telephone number is (571)272-9924. The examiner can normally be reached on 9:00 AM to 5:00 PM, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann R. Richter can be reached on 571-272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

NWS

/John Pak/
Primary Examiner, Art Unit 1616